REMARKS

By the present amendment, claims 1, 4, 7, 9, 10, 11, 13, 14, 17 and 27 have been amended. Applicant is providing all of the pending claims 1-30 and 41-44 as requested by the Examiner. No new matter has been entered in this amendment and its entry is respectfully requested.

The Official Action dated December 4, 2001 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Claim Objections

Claim 1 was objected to because the term "transforming a host cell an expression vector" was grammatically incorrect. In response, claim 1 has been amended in order to replace the phrase under objection with "transforming a host cell with an expression vector".

Claim 27 was objected to because the sequence identifiers were incorrect. In response, claim 27 has been amended in order to recite "SEQ ID NO:1" and "SEQ ID NO:3".

35 U.S.C. §112, second paragraph

The Examiner has objected to claims 1-30 and 41-44 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. We will address each of the objections raised by the Examiner in the order which they appear in the office action.

The Examiner has objected to claims 1, 20, 41 and 42 as being indefinite in the recitation of "an nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen". The Examiner further states that it is "unclear as

to whether said nucleic acid encodes only a pro-peptide or further encodes the mature form of the zymogen". We respectfully disagree with the Examiner as the language used in these claims is clear in specifying that nucleic acid sequence (a) encodes only a pro-peptide derived from an autocatalytically maturing zymogen. The term "pro-peptide" is clearly defined in the application on page 5, lines 24 and 25. However, we point out that the language used in these claims does not exclude the possibility that the mature form of the zymogen is present in the chimeric nucleic acid sequence due to the word "comprising" that precedes the recitation of the specific components of the chimeric nucleic acid sequence. Claims 6, 25 and 44 are included to specify an embodiment where the chimeric nucleic acid sequence does not include the mature form of the zymogen.

The Examiner has objected to claims 1-3, 21-23 and 41-42 as being indefinite in the recitation of "derived from". The term "derived from" is meant to include a pro-peptide that is part of or isolated from an autocatalytically maturing zymogen as well as any mutant forms or variants of a pro-peptide derived from an autocatalytically maturing zymogen. In this regard, we refer to page 11, lines 24-34 of the application. We submit that these claims are clear as written.

The Examiner has objected to claim 4 due to the term "group comprising". As the Examiner has suggested, we have replaced this term with the proper term "group consisting of".

The Examiner has stated that claims 10, 11, 16 and 17 are confusing in the recitation of "*in vivo* conditions". We agree with the Examiner that the term "*in vivo*" means "within the living body" and these claims are meant to cover such an embodiment. With respect to Example 3 at page 17, we submit that it is not stated that using a gut extract is an *in vivo* condition but rather that the use of the gut extract is support that the cleavage of the carp growth hormone could be effected *in vivo*.

The Examiner has objected to claims 11 and 17 as being indefinite in the recitation of "conditions are those prevalent in a tissue of bodily fluid of an animal". In response, these claims have been amended in order to specify that in vivo conditions "take place" in a tissue or a bodily fluid of an animal.

In view of the foregoing, we respectfully request that the objections to the claims under 35 U.S.C. §112, second paragraph be withdrawn.

35 U.S.C. §112, first paragraph

The Examiner has objected to claims 1-30 and 41-44 under 35 U.S.C. §112, first paragraph as lacking enablement for a method for preparing a recombinant polypeptide by transforming a host cell with a nucleic acid encoding any pro-peptide derived from an autocatalytically maturing zymogen (claim 1), any protease (claim 2), or any aspartic, serine or cysteine protease (claim 3) upstream of a nucleic acid encoding a heterologous polypeptide, expressing the encoded fusion protein and altering the environment using any conditions (claim 1) or any pH, salt, or temperature conditions (claim 7) in order to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequence encoding therefor and compositions thereof. We respectfully disagree with the Examiner for the reasons that follow.

By the present amendment, claim 1 has been amended in order to specify that a mature form of an autocatalytically maturing zymogen is added to the fusion protein in step c) of the method. This amendment further clarifies the conditions required to "alter the environment of the fusion protein" in order to result in the cleavage of the pro-peptide and the release of the recombinant polypeptide. However, we submit that further limitation of the claims in order to specify other conditions that are altered is not necessary and could readily be determined by one of skill in the art. As we have previously submitted, one of skill in the art having chosen a particular pro-peptide/heterologous protein combination would readily be able to determine the optimal conditions for the cleavage reaction.

One of skill in the art could also readily use any pro-peptide in the methods of the invention. In this regard, we refer to page 10, line 11 to page 11, line 33 wherein the application clearly supports and provides guidance on how to use any pro-peptide in the methods of the invention.

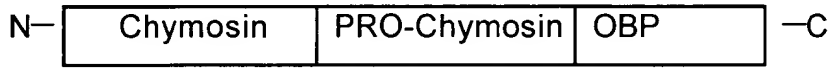
In view of the foregoing, we respectfully request that objections to the claims under 35 U.S.C. §112, first paragraph, be withdrawn.

35 U.S.C. §102/103

The Examiner has objected to claims 1-7, 9-13, 15-26, 28-30 and 41-44 under 35 U.S.C. §102(a) as being anticipated by or, in the alternative, under U.S.C §103(a) as obvious over Moloney (WO 96/21029). We respectfully disagree with the Examiner for the reasons that follow.

The Moloney application teaches a nucleic acid construct comprising a nucleic acid encoding an oil body protein (OBP) linked to a nucleic acid including a heterologous protein. In one embodiment, the heterologous protein can be chymosin which would result in the preparation a fusion protein that can be shown schematically as:

The Examiner appears to be suggesting that Moloney teaches the preparation of the following fusion protein:



However, we submit that this would require preparing a construct in which the pro-sequence is separated from and appears downstream from the mature chymosin sequence. There would be no motivation to prepare such an altered zymogen sequence in Moloney. Further, even if one were to prepare such a sequence, it would

be questionable whether or not cleavage resulting in a release of a mature chymosin would take place.

In view of the foregoing, we respectfully request that the objections to the claims under 35 U.S.C. §102 and 35 U.S.C §103 be withdrawn.

35 U.S.C. §103

The Examiner has objected to claim 8 under 35 U.S.C. §103(a) as being unpatentable over Moloney (WO 96/21029) in view of McCaman et al. (J. Biol. Chem. 261:15345-15348). We respectfully disagree with the Examiner for the reasons that follow.

Claim 8 indirectly depends from claim 1 which is patentable over Moloney for the reasons stated above. The deficiencies in Moloney are not remedied by McCaman which does not teach or remotely suggest the method of the invention. McCaman teaches that the zymogen form of chymosin is activated at pH 2 to form a pseudochymosin product that is further processed to chymosin at pH 4.5.

The Examiner has objected to claim 27 under 35 U.S.C §103(a) as being unpatentable over Moloney (WO 96/21029) in view of Fine et al. (Gen Comp Endocrinol 89:51-61). We respectfully disagree with the Examiner for the reasons that follow.

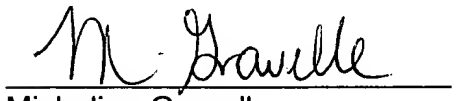
Claim 27 indirectly depends from claim 20 which is patentable over Moloney for the reasons stated above. The deficiencies in Moloney are not remedied by Fine et al. Fine et al. teach the nucleic sequence of carp growth hormone. Fine et al. do not teach or suggest a chymosin pro-peptide-hirudin fusion protein.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to discuss the matter, he is kindly requested to contact Micheline Gravelle at 416-957-1682 at his convenience.

Respectfully submitted,

Maurice Moloney, Joenel Alcantara and Gijs van Rooijen



Micheline Gravelle
Registration No. 40,261

Bereskin & Parr
Box 401, 40 King Street West
Toronto, Ontario, Canada
M5H 3Y2

(416) 364-7311

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

As requested by the Examiner, all of the pending claims are provided below. We point out that only claims 1, 4, 7, 9, 10, 11, 13, 14, 17 and 27 have been amended by the present amendment.

1. (Twice Amended) A method for the preparation of a recombinant polypeptide comprising

a) transforming a host cell with an expression vector comprising:

(1) a nucleic acid sequence capable of regulating transcription in a host cell, operatively linked to

(2) a chimeric nucleic acid sequence encoding a fusion protein, the chimeric nucleic acid sequence comprising (a) a nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen, linked in reading frame to (b) a nucleic acid sequence heterologous to the pro-peptide and encoding the recombinant polypeptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the pro-peptide; operatively linked to

(3) a nucleic acid sequence encoding a termination region functional in said host cell,

b) growing the host cell to produce said fusion protein; and

c) adding a mature form of an autocatalytically maturing zymogen to the fusion protein [altering the environment of the fusion protein] so that the pro-peptide is cleaved from the fusion protein to release the recombinant polypeptide.

2. A method according to claim 1 wherein said pro-peptide is derived from a protease.

3. A method according to claim 1 wherein said pro-peptide is derived from an aspartic protease, a serine protease or a cysteine protease.

4. (Amended) A method according to claim 1 wherein said pro-peptide is derived from a zymogen selected from the group [comprising] consisting of chymosin, trypsinogen, pepsin, HIV-1 protease, pepsinogen, cathepsin [or] and yeast proteinase A.

5. A method according to claim 1 wherein the recombinant polypeptide is hirudin or carp growth hormone.

6. The method according to claim 1 wherein the chimeric nucleic acid sequence does not include a sequence encoding a mature form of the zymogen.

7. (Amended) A method according to claim 1 which further [wherein the altering the environment] comprises altering the pH, altering the salt concentration or altering the temperature in step (c).

8. A method according to claim 7 wherein the altering the pH comprises altering the pH to a pH from about 2 to about 4.5.

9. (Amended) A method according to claim 1 wherein step (c) [the altering the environment] takes place under in vitro conditions.

10. (Amended) A method according to claim 1 wherein step (c) [said altering the environment] takes place under in vivo conditions.

11. (Amended) A method according to claim 10 wherein the in vivo conditions take place [are those prevalent] in a tissue or bodily fluid of an animal.

12. A method according to claim 11 wherein the tissue or bodily fluid comprises the milk, blood, the stomach, the gut or the kidneys of said animal.

13. (Amended) A method according to claim 1 wherein [a] the mature form of [an] the autocatalytically maturing zymogen [is] added in step (c) [wherein said zymogen] is homologous to the pro-peptide.

14. (Amended) A method according to claim 1 wherein [a] the mature form of [an] the autocatalytically maturing zymogen [is] added in step (c) [wherein said zymogen] is heterologous to the pro-peptide.

15. The method according to claim 13 wherein the mature zymogen is added under in vitro conditions.

16. The method according to claim 13 wherein the mature zymogen is added under in vivo conditions.

17. (Amended) The method according to claim 16 wherein said in vivo conditions take place [are those prevalent] in a tissue or bodily fluid of an animal.

18. The method according to claim 17 wherein the tissue or bodily fluid is a stomach, kidney, gut, blood or milk of said animal.

19. A method according to claim 1 wherein said nucleic acid sequences are deoxyribonucleic acid (DNA) sequences.

20. A chimeric nucleic acid sequence encoding a fusion protein comprising (a) a nucleic acid sequence encoding a pro-peptide from an autocatalytically maturing zymogen and (b) a nucleic acid sequence encoding a polypeptide that is heterologous to the pro-peptide.

21. A chimeric nucleic acid sequence according to claim 20 wherein the pro-peptide is derived from a protease.

22. A chimeric nucleic acid sequence according to claim 20 wherein the pro-peptide is derived from a serine protease, aspartic protease or a cysteine protease.

23. A chimeric nucleic acid sequence according to claim 20 wherein the pro-peptide is derived from chymosin, trypsinogen, pepsin, HIV-1 protease, pepsinogen, cathepsin or yeast proteinase A.

24. A chimeric nucleic acid sequence according to claim 20 wherein the polypeptide is hirudin or carp growth hormone.

25. A chimeric nucleic acid sequence according to claim 20 which does not include a sequence encoding a mature form of the zymogen.

26. A chimeric nucleic acid sequence according to claim 20 wherein said nucleic acid sequences are deoxyribonucleic acid (DNA) sequences.

27. (Amended) A chimeric nucleic acid sequence according to claim 26 wherein the chimeric sequence is as shown in [SEQ.ID.NO 1.] SEQ ID NO:1 or [SEQ. ID. NO. 3] SEQ ID NO:3.

28. An expression vector comprising a chimeric nucleic acid sequence according to claim 20 and a regulatory sequence suitable for expression in a host cell.

29. A transformed host cell containing an expression vector according to claim 28.

30. A transformed host cell containing an expression vector according to claim 28 wherein the host cell is a bacterial cell, a fungal cell, a plant cell or an animal cell.

41. A pharmaceutical composition comprising a chimeric nucleic acid sequence encoding a fusion protein, the chimeric nucleic acid sequence comprising (a) a first nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen and (b) a second nucleic acid sequence encoding a polypeptide that is heterologous to the pro-peptide.

42. A food composition comprising a chimeric nucleic acid sequence encoding a fusion protein, the chimeric nucleic acid sequence comprising (a) a first nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen and (b) a second nucleic acid sequence encoding a polypeptide that is heterologous to the pro-peptide.

43. A composition according to claim 41 wherein the nucleic acid sequences are deoxyribonucleic acid (DNA) sequences.

44. A composition according to claim 41 wherein said chimeric nucleic acid sequence does not include a sequence encoding a mature form of the zymogen.